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EXAMINER	
SIDBERRY, H	
ART UNIT	**PAPER NUMBER**
1801	8

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DATE MAILED: 02/05/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 6/6/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474..
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1—18 are pending in the application.
   Of the above, claims 1-14, 18 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1—10, 15—17 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The amendment filed 3/31/97, under 37 C.F.R. 1.116 in response to the final rejection has been considered but is not deemed to place the application in condition for allowance and will not be entered because:

(1) The proposed amendment raises new issues that would require further consideration and/or search.

Applicant has amended claim 1 to now recite actively or passively immunizing. This amendment raises issues of enablement as the specification does not establish that antibody to the non-covalent complex (idiotypic antibody) when administered to a host will effect protection against heterologous gram-negative bacteria or endotoxin-mediated pathology.

Applicant has amended the claim to now recite actively or passively immunizing a subject against infection by heterologous Gram-negative bacteria This amendment raises further scope and enablement issues, as the specification does not establish that the non-covalent complex effects protection against "heterologous" gram-negative bacteria.

(2) The proposed amendment raises the issue of new matter.

Applicant has amended claim 1 to recite "wherein the antibody produced by said vaccine is not bacteriocidal". This negative limitation is considered new matter, as the specification, Example 9, indicates that "the post-immune sera from the rabbits of Example 8 was bacteriocidal." As shown in Table 4, this vaccine elicited significant increases (4 to 32-fold) in bactericidal titer against both homologous and heterologous strains". Example 8 shows rabbits immunized with the J5 DLPS-NMGBOMP non-covalent complex vaccine. The amendment to include this limitation raises issues of 112 1st paragraph new matter issues, as the specification clearly indicates that the complex induces bacteriocidal antibodies. If Applicant continues with this limitation, then the limitation would raise further issues that specification does not teach how to obtain "antibodies which are not bacteriocidal" using the complex.

Further claim 1 has been improperly amended by Applicant to include the limitation (ii) a purified, "detoxified" outer membrane protein (OMP). The limitation "detoxified" has been improperly

inserted in the claim, and is not been properly indicated to be amendatory material by underlining. This limitation is "new matter".

(3) The proposed amendment(s) are not deemed to place the application in better form for appeal by materially simplifying the issues for appeal, in view of the substantive issues they raise.

(4) The requested amendment to claim 5, at line 2 cannot be acted on as the term "endotoxin" does not occur on line 2.

As Applicants' amendment will not be entered, the Examiner's response will be directed to the unamended claims.

(a) The objection to the specification and the rejection of claims 1-3, 5-10, 15-17 under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure, failing to provide an adequate written description of the invention, failing to teach how to make and/or use the invention is maintained.

Applicant has submitted a Declaration from Dr. S. Opal which is not properly executed and Declaration from Dr. A. Cross.

Dr. Opal discusses examples where the neutropenic rat model was used for studies of other potential vaccines that have progressed to human clinical trial in the declaration. They are: HA-IA monoclonal antibody, anti-lipid A antibody, E5, BPI and IL-1 receptor antagonist. These examples do not appear to be analogous to the non-covalent complex of detoxified LPS and OMP, as they are examples of monoclonal antibody (passive immunization) or "antibiotic"-like compound (BPI), assayed in neutropenic rat, none of which requires the host to induce an immune response to the agent administered.

Dr. Opal concludes by stating "in my opinion the neutropenic rat is the art-recognized animal model for gram-negative sepsis studies." This conclusionary statement is not supported any objective evidence, such as publications which show this animal model used in active immunization, and challenge experiments.

The declaration of Dr. Cross has been considered.

Dr. Cross contends that the present invention protects against heterologous infections, citing page 20 and 22 of the

specification.

This limitation, as discussed above raises issues of scope under 35 USC 112 1st paragraph.

Page 20 shows cross-reactivity of IgG from post-immune serum and references Table 5. Table 5 shows in vitro binding of the serum to various bacteria which have been treated with Imipenem, but does not show any animals immunized with the complex and subsequently challenged with these bacteria, to enable the claim of "effective in actively immunizing against infection" or the "cross-protection" that Dr. Cross asserts in the declaration. Mere antibody binding to bacteria does not translate into protection using the complex.

In the declaration Dr. Cross addresses the rejections set forth in Paper No. 13.

However, as the amendment will not be entered, the remarks directed to the claims which do not contain these limitations are not considered as relevant

Applicants claims are not limited to sepsis, but recite "infection by gram-negative bacteria and LPS endotoxin-mediated pathology" which encompasses those which may or may not have a bacterial foci. Applicants statement that the "examiner has cited no reference to support her doubts about the value of the neutropenic rat as model is not correct, as Cross et al and Green et al were cited.

Applicant further contends that the Examiner doubts the "utility" of the neutropenic rat.

The Examiner has not doubted the "utility" of the neutropenic rat, but indicated that the neutropenic rat and/or the rabbit appeared not to be correlative or predictive of successful treatment in humans. Applicants have presented no evidence to traverse this.

Applicant also urges that the "declarant describes contractual arrangements with pharmaceutical companies to use the present neutropenic rate model to test their products for potential use in human clinical trials," and this serves to validate the animal model.

This is not persuasive as Applicant's claims are not directed to the neutropenic rat.

Further, the examples cited by Dr. Opal use monoclonal antibody (passive therapy) or an antibiotic-like compound (BPI) which do not require the host to mount an immune response to the vaccine.

The Declarations further do not address LPS endotoxin mediated pathology as of the claims.

The asserted evidence is not commensurate in scope with the claims, and therefore is not sufficient to address the 112, 1st paragraph rejection.

(b) The rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Zollinger et al US Patent 4 707 543 is maintained for reasons of record.

(c) The rejection of claims 1-3, 5-10, 15-17 under 35 U.S.C. § 103 as being unpatentable over Zollinger et al US Patent 4 407 543 for reason of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to H. Sidberry whose telephone number is (703) 308-0170.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to the Group 1800 by facsimile transmission. The CM1 1802 Fax Center number is (703 308-4242).

Sidberry/hfs
May 13, 1997

HARRY F. SIDBERRY
PRIMARY EXAMINER
GROUP 1800

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The examiner acknowledges the response filed 7/30/96 amending claims 1, 5, 6, 9 and 15.

Claim 4 has been cancelled.

Claims 1-3, 5-10, 15-17 are under examination.

Claims 11-14, 18 were previously withdrawn from further consideration under 37 CFR 1.1142(b) as being directed to a non-elected invention, election considered as being made without traverse in Paper No. 5.

(a) The rejection of claims 1-3, 5-10, 15-17under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of Applicant's remarks.

Applicant's arguments filed 7/30/96 have been fully considered but they are not deemed to be persuasive.

(1) The objection to the specification and the rejection of now claims 1-3, 5-10, 15-17 under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure, failing to teach how to make and/or use the invention is maintained.

Applicant contends that the 112 1st paragraph is a "lack of utility rejection thinly disguised as a rejection on nonenablement grounds". Applicant further contends that "the Examiner cites older references that do not reflect the state of the current art".

It is noted that the Examiner acknowledges Applicants statement of "utility", as no rejection under 35 USC 101 has been set forth.

Applicant's claim a method of immunizing against gram-negative infections and against Group B meningococcal disease.

The specifications sets forth data using rabbits and the neutropenic rat demonstrating the induction of bactericidal antibody and protection against P.aeruginosa challenge, respectively.

However, it is not clear if the rabbit is an art recognized animal model of Group B meningococcal disease which correlates and is predictive of similar activity in humans.

Mandrell et al, cited, indicates that the immungenicity of meningococcal proteins in animals and their antigenicity with animal antibodies would not prove that the proteins have analogous activities in humans, as differences in the functional activities of human and animal antibodies induced by meningococcal proteins have been reported.

Moreno et al also indicate that "one should be cautious,...in attempting to extrapolate the protective value of this (Group B OMP complexed to purified B polysaccharide) from mouse models to human system(s)". (see page 532, left side)

Applicant's also claim the complex to effect protection against gram-negative bacteria or against LPS mediated pathology".

The terms infection by gram-negative and LPS mediated pathology are broadly encompassing and includes any pathological condition activated by LPS.

It is not clear if the neutropenic rat is an art accepted animals model for the generically claimed gram-negative bacteria and LPS mediated pathology.

Greenman et al, cited, teach that aside from antibiotic, surgical, and supportive care, no specific pharmacotherapy is available for gram-negative sepsis or associated organ failure.

The Examiner has further considered Applicants' submitted exhibits, however none of the exhibits appears to support Applicant's assertions that the neutropenic rat ia an animal

model for the broadly claimed vaccine and method to immunize against Group B meningococcal disease; infections by gram-negative bacteria and LPS mediated pathology.

Applicant contends that the Examiner has not demonstrated that one skilled in "this art" would find incredible the predicative value of applicants' neutropenic rat model.

Applicants claims are directed to vaccine which effects protection against group B meningococcal disease and "gram-negative" bacteria.

Applicant maintains that "vaccines have been developed against poliomyelitis, meningococcus infection, pertussis and hepatitis B infection."

The Examiner notes that existence of an "animal model" for pertussis, and the presence of "vaccines" against polio. The "vaccine" against meningococcal disease is polysaccharide protein based against serotypes A and C, not serotype group B.

However, Applicants claims are not directed to these pathogens, but to group B meningococcal disease, for which there is no vaccine and the broad vaccine "against gram-negative bacteria" which is not enabled by the specification.

Applicant has submitted various articles to traverse the issue of "animal models" raised in the 35 USC 112 1st rejection.

Exhibit 1 has been considered, however, it is unclear how this exhibit addresses the rejection of the claims under 35 USC 112, 1st paragraph. It appears to support the Examiner's position that the "LPS-mediated pathology" is a broadly generic term, as "the biologic effects are defined to include "shock, fever, leukopenia, hypoglycemia, and intravascular coagulation.".

Exhibit 3 is directed to "Future Sepsis Research" which indicates that from a "practical perspective, animal models provide insights about specific components of the septic process but cannot truly mimic the full clinical complexity and intrinsic

heterogeneity of septic patients". (see page 11 of Future of Sepsis Research)

Cross et al, was cited by the Examiner and now submitted by Applicant, does not support Applicants assertions that the "neutropenic rat is generally accepted as an animal model for determining efficacy of vaccines for immunotherapy against gram-negative bacteria and endotoxin-mediated pathology."

Cross et al does not discuss the neutropenic rat, and further states, "since animal species differ considerably in their cardiocular physiology and susceptibility to bacterial endotoxin, investigators [should] carefully considered the relative merits and limitations of each animal model before extrapolating animal data to clinical efficacy in septic patients." (see page 2741)

Romulo et al is directed to the use of monoclonal antibody directed to endotoxin or passive therapy and not the use of a complex for active immunization.

The issue regarding claim 1 which originally recited LPS, but now recites "detoxified" is resolved.

(2) The rejection of claim 1 under 35 U.S.C. § 102(b) as being anticipated by Zollinger et al US Patent 4 707 543 is maintained.

Applicant has amended claim 1 to now recite that the lipopolysaccharide is detoxified.

However, Zollinger et al disclose complexes which may be comprised of detoxified LPS and purified OMP from N. meningitidis.

Applicant has submitted no evidence which documents a material structural and functional difference between the claimed complex and that of Zollinger et al.

(3) The rejection of claims 1-3, 5-10, 15-17 under 35 U.S.C. § 103 as being unpatentable over Zollinger et al US Patent 4

707 543 is maintained. Applicant has now amended claim 1 to recite detoxified LPS.

Applicants contend that Zollinger et al does not disclose a purified and detoxified LPS derived from E. coli and a purified OMP from N. meningitidis.

Zollinger et al disclose the use of detoxified (polysaccharide) LPS-OMP non-covalent complexes. The term "polysaccharide", according to Zollinger et al includes lipolysaccharide and capsular polysaccharide. (see column 2, lines 25-29. The detoxified lipopolysaccharide outermembrane complexes can be either noncovalently or covalently bond to form the complex. (see column 4, lines 15-22) The detoxified LPS can be derived from gram-negative bacteria, including E. coli. (see column 4, liens 25-29) The outer membrane protein being derived from N. meningitidis from serotype B. (see column 5, Example 1)

Thus, the teachings of Zollinger et al clearly suggest to one of ordinary skill in the art, the non-covalently complexing of detoxified LPS derived from gram-negative bacteria and OMP from Neisseria meningitidis serotype B.

Applicant contends that the Examiner "appears not to have appreciated the distinction between the Zollinger et al patent and the present invention."

Applicant maintains that Zollinger et al is directed primarily to the process for preparing polysaccharide-OMP complexes and to testing the bactericidal activity. "The present invention is directed to the immunoregulatory properties of a complex comprising a purified, detoxified J5 LPS and purified OMP from N. meningitidis, said properties consisting of active or passive immunization of a subject against Gram-negative bacteria and LPS-mediated pathology. Only the present J5 LPS endotoxin works in this respect".

Applicant contends that Zollinger et al proposed that an OMP-LPS vaccine would generate type-specific antibodies against meningococci that would be bactericidal for that one serotype. Applicant urges that the properties of Zollingers's complex are characterized by: the induction of type-specific antibody that can (2) enhance the killing of type-specific bacteria and utlimatlely to (3) prevent infection."

Applicant contends that the J5 subunit vaccine in the present invention is therefore entirely different is not suggested by Zollinger et al, because the invention provides antibodies that provide protection against the biologic activities of heterologous LPS and do not kill bacteria.

Applicant further urges that the "properties of the invention (the LPS-OMP complex) is "different" from that of Zollinger's. However, the claims do not contain these asserted "critical" limitations directed to the properties of the complex.

Moreover, it is noted that Zollinger et al indicate that the complexes may be used to protect against infection by the bacteria, as does Applicant.

Applicant further contends that the properties of the claimed complex are not "bactericidal", however, page 18 of the specification indicates that "bactericidal antibody response" was determined for Applicants' complex. This would appear to be contrary to Applicants remarks. It is also noted that the claims include the recitation of "actively immunizing a subject against infection by gram-negative bacteria or against lipopolysaccharide endotoxin-mediated pathology", which is not bactericidal related.

Applicant further contends, at page 11 of the remarks, that "another aspect of the present invention is evident in the demonstration that this purified and detoxified J5 LPS induces antibodies that can mediate protection independently of whole

serum, and that the IgG isotype that predominates in commercially available gammaglobulin preparations can provide protection."

It is again noted the claims do not include these asserted limitations.

It is the Examiner's position that the teachings of Zollinger et al render the claimed invention as obvious.

Zollinger et al suggest the use of detoxified LPS which may be obtained from E. coli, and non-covalently complexed with OMP from N. meningitidis serotype B as a vaccine against infection.

Although Zollinger et al does not teach the LPS to be derived from J5, the teachings of Zollinger suggest that similar results may be attained using any detoxified LPS obtained from other bacteria, as Zollinger et al indicate that "the process of this invention is generally applicable to the preparation of detoxified LPS (polysaccharide)-protein complexes derived from gram-negative bacteria, such as E. coli".

Applicant has not presented any remarks which are persuasive regarding the above maintained rejections.

The Examiner has considered the IDS submitted 1/23/96, however, no 1449 appears to have been submitted with the cited references.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE

STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry of a general nature or relating o the status of this application should be directed to the Group receptionist whose telephone number is (703)-308-0196.

1. Any inquiry concerning this communication or earlier communications from the examiner should be directed to H. F. Sidberry whose telephone number is (703) 308-0170.

Sidberry/hfs
October 23, 1996

HAZEL F. SIDBERRY
PRIMARY EXAMINER
GROUP 1800

Applicant's election of Group I, claims 1-10, 15-17, in Paper No. 5, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse. See M.P.E.P. 818.03(a).

Claims 11-14, 18 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b), as being drawn to a nonelected invention. Election was considered made **without** traverse in Paper No. 5.

Claims 1-10, 15-17 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 6 are vague and indefinite in the recitation of lipopolysaccharide endotoxin mediated pathology". It is unclear what Applicant is defining.

Claims 1, 4, 5, 9, 15, are indefinite in the recitation of lipopolysaccharide endotoxin. The use of lipopolysaccharide to modify endotoxin is considered redundant.

Claims 2, 7 16 are indefinite in the recitation of Jr (Rc chemotype). The use of J5 modified by Rc chemotype is considered redundant.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure, failing to teach how to make and/or use the invention.

Applicant claims are directed to a vaccine of comprised

noncovalent complex of LPS and OMP.

Applicant claims a method to immunize against gram-negative infections and against Group B meningococcal disease.

The specification sets forth data using the rabbits, demonstrating the induction of bactericidal antibody.

However, it is not clear if the rabbit is an art recognized animal model of Group B meningococcal disease, which correlates and is predictive of similar activity in humans.

Mandrell et al (Infection and Immunity 57:1590-1589, 1989) indicate that the immunogenicity of meningococcal proteins in animals and their antigenicity with animal antibodies would not prove that the proteins have analogous activities in humans, as differences in the functional activities of human and animal antibodies induced by meningococcal proteins have been reported. (see page 1596)

Moreno et al (Infection and Immunity 47:527-533, 1985) in a study of the immunity and protection against N. meningitidis using Group B OMP complexed to purified B polysaccharide, indicated that "one should be cautious, however, in attempting to extrapolate the protective value of this vaccine from mouse models to human system". (see page 532, left side)

Applicant also claims the complex to effect protection against Gram-negative bacteria or against "lipopolysaccharide endotoxin-mediated pathology".

The terms "infection by Gram-negative bacteria" and "endotoxin pathology" is broadly encompassing and includes any "pathological" condition activated by LPS.

The specification sets forth data using the neutropenic rat model and induction of bactericidal antibody in rabbits.

However, it is not clear if the neutropenic rat is an art accepted animal model for the generic Gram-negative bacteria and "endotoxin mediated pathology", from which one could reasonably extrapolate to similar efficacy in humans.

Greenman et al (JAMA 266:1097-1102, 1991) teach that "aside from antibiotic, surgical, and supportive care, no specific

pharmacotherapy is available for gram-negative sepsis or associated organ failure". (see page 1097)

Cross et al (Infection and Immunity 61:2741-2747, 19930 indicates that "experimental data derived from animal research have been and will continue to be indispensable in the development of new therapeutic strategies for sepsis. The use of animal models of sepsis can provide invaluable information of the safety, efficacy and pharmacokinetics of immunotherapeutic agents". (see page 2741) Cross et al continues by stating that most animal models represent intoxication with bacteria as opposed to sepsis, cautioning that distinctions should be made between models of intoxication and infection in order to properly evaluate the efficacy or potential toxicity of treatment regimens for sepsis". (see page 2744)

Further, Cross et al teach that "since animal species differ considerably in their cardiovascular physiology and susceptibility to bacterial endotoxin, investigators [should] carefully consider the relative merits and limitations of each animal model before extrapolating animal data to clinical efficacy in septic patients. (see page 2742, last paragraph left side)

Cross et al (Journal of Endotoxin Res. 1:57-69, 1994) indicates that "presently there are no adequate widely accepted animal models that reflect the septic process in humans". (see page 63, 1st paragraph) And "additionally, [in] models that need to comprised the animal host defenses in order to enhance susceptibility .....it would be difficult to extrapolate". (see page 63)

Calandra et al (The Journal of Infectious Dis. 158:312-319, 1988) indicate that "despite successes in animal models, well designed clinical trials using either high-dose corticosteroids or naloxone have failed to demonstrate an increased survival of patients with septic shock". (see page 312)

Thus, the results in animal models do not necessarily correlate and predict similar efficacy in humans.

Applicant's claim 1 is directed to a complex comprising LPS and OMP. It is known in the art that LPS is toxic. The specification

shows only the use of detoxified LPS used in the complex. Note the specification indicates treatment of the E. coli LPS with either alkaline or sonication, etc which would yield a detoxified LPS. Note the statement, in Example 1, "in view of the fact that native J5 LPS was pyrogenic in the rabbit pyrogenicity test at a dose of 0.01 ug, it was necessary to prepare a detoxified J5 LPS for use in making a J5 DLPS-BGOMP non-covalent complex vaccine." In view of these statements, it is viewed that the specification does not provide enablement for the E. coli LPS-GBOMP complex, as it does not teach how to use the complex as a vaccine.

Claims 1-10, 15-17 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless--

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this country or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for pat nt.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this

section made in this Office Action:

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> **A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.**
>
> **Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligations under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claim 1 is rejected under 35 U.S.C. § 102(b) as being anticipated by Zollinger et al US Patent 4 707 543.

Zollinger et al US Patent 4 707 543 disclose complexes comprised of LPS and purified OMP from N. meningitidis. (see column 1)

Claims 1-10, 15-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Zollinger et al.

Zollinger et al US Patent 4 707 543 teach the use of detoxified LPS from detoxified polysaccharide outer membrane complexes from those bacteria, as vaccines to protect animals against infections. The term polysaccharide includes lipopolysaccharide and capsular polysaccharide. (see column 2, lines 25-29) The detoxified

lipopolysaccharide outermembrane complexes where capsular polysaccharide can be either bonded noncovalently or covalently to the protein to form a complex. (see column 4, lines 15-22) The detoxified polysaccharide complexes being derived from gram-negative bacteria, including Escherichia coli. (see column 4, lines 25-29) The outer membrane protein being derived from N. meningitidis from serotype B. (see column 5, Example 1)

Although Zollinger et al does not teach the LPS to be derived from the J5 strain, Zollinger et al suggest the use of detoxified LPS from E. coli in a noncovalent complex with outer membrane from N. meningitidis.

The teachings of Zollinger et al suggest that similar results may be attained using any complex comprising a detoxified LPS and N. meningitidis OMP, as "the process of this invention is generally applicable to the preparation of detoxified polysaccharide-protein complexes derived from gram-negative bacteria, such as E. coli."

The Art Unit location of your application in the Patent and Trademark Office has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1802

Any inquiry concerning this communication or earlier communications from the examiner should be directed to H. Sidberry whose telephone number is (703) 308-0170.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to the Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 1802 fax Center number is (703-308-4065)

Sidberry/hfs
January 22, 1996

HAZEL F. SIDBERRY
PRIMARY EXAMINER
GROUP 1800

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-10, 15-17, drawn to vaccine comprising LPS from E. coli and OMP from N. meningitidis and a method of actively immunizing a host, classified in Class 424, subclasses 184.1, 193.1, 203.1, 250.1.

II. Claims 11-14, 18, drawn to antibody composition and a method of passive therapy, classified in Classes 424 and 530, subclasses 130.1, 137.1, 164.1 and 387.1, 388.4.

The inventions are distinct, each from the other because of the following reasons:

The Inventions of Group I and II are directed to two methods which differ in method steps, parameters and reagents used.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and divergent subject matter, and because the searches for the individual Groups are not coextensive, restriction for examination purposes as indicated is proper.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to H. Sidberry whose telephone number is (703) 308-0170.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to the

Group 1800 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 1813 Art Unit fax Center number is (7030 305-7939)

HAZEL F. SIDBERRY
PRIMARY EXAMINER
GROUP 1800

5 Sidberry/hfs
April 7, 1995